PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SWABEY OGILVY RENAULT
1981 McGill College Avenue
Suite 1600
Montréal, Québec H3A 2Y3
CANADA

DUE ON SEP 2 1 2000
Short Term

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	21.06.2000
REPLY DUE	**within 3 month(s)** from the above date of mailing

Applicant's or agent's file reference	International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
13424-1PCT CC	PCT/CA99/00572	17/06/1999	17/06/1998

International Patent Classification (IPC) or both national classification and IPC
C12N15/11

Applicant
RECHERCHES EXPERTISES ET DEVELOPPEMENT ... et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 17/10/2000.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized officer / Examiner
Page, M

Formalities officer (incl. extension of time limits)
Vullo, C
Telephone No. +49 89 2399 8061

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-39 as originally filed

Claims, No.:

1-9 as originally filed

Drawings, sheets:

1/29-29/29 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons

and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 2, 4, 6-9: NO 3, 5: YES
Inventive step (IS)	Claims	1, 2, 4-9: NO 3: YES
Industrial applicability (IA)	Claims	1-5: YES 7-9:*

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item IV
Lack of unity of invention

The separate inventions/groups of invention are:

1) Oligonucleotides directed against a nucleic acid encoding the CCR3 receptor: Claims 1, 5-9 (all partially) and claim 4.

2) Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-4 and IL-13 receptors: Claims 1, 5-9 (all partially) and claim 2.

3) Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1, 5-9 (all partially) and claim 3.

In the absence of any common special technical features, these groups of inventions are not considered to be linked as to form a single general inventive concept (Rule 13.1 PCT). The use of antisense oligonucleotides in suppressing the expression of chemokine receptors cannot be regarded as such a feature because this use has been well documented in the prior art.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The application concerns the provision of antisense oligonucleotides against diverse interleukin receptors for the treatment of various diseases.

1) Reference is made to the following documents:
D1: WO 96 22371 A (BRIGHAM & WOMENS HOSPITAL ;LEUKOSITE INC (US); PONATH PAUL D (US);) 25 July 1996 (1996-07-25)
D2: IKIZAWA K ET AL: 'INHIBITION OF IL-4 RECEPTOR UP-REGULATION ON B CELLS ANTISENSE OLIGODEOXYNUCLEOTIDE SUPPRESSES IL-4-INDUCED HUMAN IGE PRODUCTION' CLINICAL AND EXPERIMENTAL

IMMUNOLOGY, vol. 100, no. 3, 1995, pages 383-389, XP000561859 ISSN: 0009-9104

D3: WO 97 20926 A (SANOFI SA ;CAPUT DANIEL (FR); FERRARA PASCUAL (FR); LAURENT PATRIC) 12 June 1997 (1997-06-12)

D4: WO 97 28190 A (MEDVET SCIENCE PTY LTD ;LOPEZ ANGEL (AU); BAGLEY CHRISTOPHER (AU);) 7 August 1997 (1997-08-07)

D5: WO 97 23244 A (SMITHKLINE BEECHAM CORP ;WEN WU DING (US)) 3 July 1997 (1997-07-03)

D6: WO 97 41154 A (DAUGHERTY BRUCE L ;DEMARTINO JULIE A (US); SICILIANO SALVATORE J () 6 November 1997 (1997-11-06)

D7: PONATH P D ET AL: 'MOLECULAR CLONING AND CHARACTERIZATION OF A HUMAN EOTAXIN RECEPTOR EXPRESSED SELECTIVELY ON EOSINOPHILS' JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, June 1996 (1996-06), pages 2437-2448, XP002056313 ISSN: 0022-1007

D8: WO 97 41225 A (INCYTE PHARMA INC ;COLEMAN ROGER (US); WILDE CRAIG G (US); AU YOUN) 6 November 1997 (1997-11-06)

2) **Novelty - Art.33(1) and (2) PCT:**

Group 1: Oligonucleotides directed against a nucleic acid encoding the CCR3 receptor: Claims 1, 5-9 (all partially) and claim 4.

Claims 1, 4 and 6-9 are not new in the light of the prior art. D1 discloses the polynucleotide sequence for CCR3 (D1 SEQ ID NO. 3), antisense oligonucleotides for this gene (page 5 lines 14-18 and claims 46 and 48) and their use in treatment of allergic disease, eosinophilia, inflammation and cancer (pages 58-60).

Claim 5 appears to be new in the light of the prior art, insofar as it applies to group 1 of the application. The SEQ ID NOs. 18-23 are new.

Group 2: Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-4 and IL-13 receptors: Claims 1, 5-9 (all partially) and claim 2.

Claims 1, 2, 6 and 7-9 are not new in the light of the prior art. D2 discloses the use of antisense oligonucleotides for the IL-4 receptor and their use in treating allergic reactions (D2 materials and methods page 384, left-hand column §2 and results pages 385-387).

Claim 5 appears to be new in the light of the prior art, insofar as it applies to group 2 of the application. The SEQ ID NOs. 1-7 are new.

Group 3: Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1, 5-9 (all partially) and claim 3.

Claims 1, 3 and 5-9 appear to be new in the light of the prior art insofar as they apply to group 3. No reference could be found to antisense oligonucleotides corresponding to the polynucleotide sequence encoding the common beta subunit of the IL-3, IL-5 and GM-CSF receptors.

3) **Inventive Step - Art.33(1) and (3) PCT:**

The following comments on inventive step are confined to subject matter which could be acknowledged as being novel.

Group 1: Oligonucleotides directed against a nucleic acid encoding the CCR3 receptor: Claims 1, 5-9 (all partially) and claim 4.

The closest prior art is document D1, which claims antisense oligonucleotides for CCR3 in order to treat allergic disease, eosinophilia, cancer or inflammation (pages 58-60 and claims 46 and 48).

In the light of the prior art, the technical problem can be regarded as the provision of antisense oligonucleotide sequences in order to decrease the expression of CCR3.

The technical problem is solved by the subject matter of claim 5, which provides antisense oligonucleotides for CCR3 (SEQ ID NOs. 18-23). These sequences appear to be obvious in the light of the disclosure of SEQ ID NO. 3 in D1: Although specific sequences have not been previously disclosed, antisense oligonucleotides are suggested in D1 (page 5 lines 14-18). It is a routine matter to then develop antisense oligonucleotides for the known polynucleic acid sequence. It can therefore not be seen where any inventive step might lie.

Group 2: Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-4 and IL-13 receptors: Claims 1, 5-9 (all partially) and claim 2.

The closest prior art is document D2, which discloses antisense oligonucleotides for the IL-4 receptor which are effective in limiting IgE production in cells stimulated with IL-4, a model for the allergic response (oligonucleotides 1-3 page 384).

In the light of the prior art, the technical problem can be regarded as the provision of alternative oligonucleotide sequences in order to decrease the expression of the common subunit of the IL-4 and IL-13 receptors.

The technical problem is solved by the subject matter of claim 5, which provides antisense oligonucleotides for the IL-4 receptor (SEQ ID NOs. 1-7). However, oligonucleotide 3 of D2 overlaps with the SEQ ID NOs. 1-3 of the present application. Inventive step cannot be acknowledged merely for alterations of previously disclosed oligonucleotide sequences in the absence of a surprising or unexpected effect. Furthermore, in light of the fact that the polynucleotide sequence for the common subunit of the IL-4 and IL-13 receptors is known, it cannot be seen how SEQ ID NOs. 4-7 can be regarded as being inventive.

Group 3: Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1, 5-9 (all partially) and claim 3.

The closest prior art is document D4, which discloses antagonists for the common beta subunit of the IL-3-, IL-5- and GM-CSF-receptor which will block the activation of these receptors (Example 2 on page 17) and are therfore useful in the treatment of allergic reactions with eosiniphilia , such as asthma, as well as leukaemic- and lymphoma-cell proliferation (page 1 lines 17-23, page 2 lines 8-16).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative mechanism for the inhibition of IL-3-, IL-5- and GM-CSF-receptor activation.

The technical problem is solved by the subject matter of claims 1, 3 and 5-9, which provide antisense oligonucleotides for the common subunit of the IL-3-, IL-5- and GM-CSF-receptors (SEQ ID NOs. 8-17). These claims appear to be inventive in the light of the prior art, which does not suggest the present solution in any way.

4) **Industrial Applicability - Art.33(1) and (4) PCT:**

For the assessment of the present claims 7-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5) **Requirements for any Amendments Art. 34(2)(b) PCT:**

Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves,

and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 13886	25.03.99	17.09.98	09.06.98

The above document discloses antisense oligonucleotides for, among other receptors, the IL-3 and IL-5 receptors (SEQ ID NOs. 1102-1115, 1159-1162, 1761-1763 and 1776-1779 and claim 10).

Re Item VII
Certain defects in the international application

a) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D8 are not mentioned in the description, nor are these documents identified therein.

b) Several references to cell amounts in the description appear to be mis-printed, e.g. page 33 line 34 "2.5x106 cells/ml". This error should be corrected for the sake of clarity (Art. 5 PCT).

PATENT COOPERATION TREATY

SWABEY OGILVY [redacted]AULT
McGILL COLLEGE
RECEIVED
OCT 1 9 2000

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

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A.M. 7 8 9 10 11 12 1 2 3 4 5 6 P.M.

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	13.10.2000
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
13424-1PCT CC	
International application No.	International filing date *(day/month/year)*
PCT/CA99/00572	17/06/1999
Priority date *(day/month/year)*	
17/06/1998	
Applicant	
RECHERCHES EXPERTISES ET DEVELOPPEMENT ... et al.	

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of tl report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Zoglauer, H Tel.+49 89 2399-8051

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
13424-1PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00572	17/06/1999	17/06/1998
International Patent Classification (IPC) or national classification and IPC		
C12N15/11		
Applicant		
RECHERCHES EXPERTISES ET DEVELOPPEMENT ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 14 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   VI ☒ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/01/2000	13.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Page, M Telephone No. +49 89 2399 7322

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00572

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,3-32,34-39	as originally filed			
2,2a-2b,33	as received on	21/09/2000	with letter of	21/09/2000

Claims, No.:

1-40	as received on	21/09/2000	with letter of	21/09/2000

Drawings, sheets:

1/29-29/29	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 10-40*.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 10-40*.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-40
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-40
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	5-7, 24-40 opinion reserved

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

The application concerns the provision of antisense oligonucleotides against diverse interleukin receptors for the treatment of various diseases.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Although the subject matter provided by claims 10-40 is considered to fall outside the scope of the claims as originally filed, in that they seek protection for compositions and methods of treatment using a combination of antisense oligonucleotides directed at different chemokine receptors, opinion is given below with regard to novelty, inventive step and industrial applicability **under the assumption that no relevant prior art exists regarding the combination of appropriate antisens oligonucleotides**. Should such prior art exist, it is probable that the opinion regarding inventive step will be revised at the regional stage.

Re Item IV

Lack of unity of invention

The separate inventions/groups of invention are:

1) Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1-9.

2) Combination of oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors and either against the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors: Claims 10-19 and 24-36.

3) Combination of oligonucleotides directed against a nucleic acid encoding the CCR3 receptor and against the common subunit of the IL-4 and IL-13 receptors: Claims 20-23 and 37-40.

In the absence of any common special technical features, these groups of inventions are not considered to be linked as to form a single general inventive concept (Rule 13.1 PCT). The use of antisense oligonucleotides in suppressing the expression of chemokine receptors cannot be regarded as such a feature because this use has been well documented in the prior art (D1, D2).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:

D1: WO 96 22371 A (BRIGHAM & WOMENS HOSPITAL ;LEUKOSITE INC (US); PONATH PAUL D (US);) 25 July 1996 (1996-07-25)

D2: IKIZAWA K ET AL: 'INHIBITION OF IL-4 RECEPTOR UP-REGULATION ON B CELLS ANTISENSE OLIGODEOXYNUCLEOTIDE SUPPRESSES IL-4-INDUCED HUMAN IGE PRODUCTION' CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 100, no. 3, 1995, pages 383-389, XP000561859 ISSN: 0009-9104

D3: WO 97 20926 A (SANOFI SA ;CAPUT DANIEL (FR); FERRARA PASCUAL (FR); LAURENT PATRIC) 12 June 1997 (1997-06-12)

D4: WO 97 28190 A (MEDVET SCIENCE PTY LTD ;LOPEZ ANGEL (AU); BAGLEY CHRISTOPHER (AU);) 7 August 1997 (1997-08-07)

D5: WO 97 23244 A (SMITHKLINE BEECHAM CORP ;WEN WU DING (US)) 3 July 1997 (1997-07-03)

D6: WO 97 41154 A (DAUGHERTY BRUCE L ;DEMARTINO JULIE A (US); SICILIANO SALVATORE J () 6 November 1997 (1997-11-06)

D7: PONATH P D ET AL: 'MOLECULAR CLONING AND CHARACTERIZATION OF A HUMAN EOTAXIN RECEPTOR EXPRESSED SELECTIVELY ON EOSINOPHILS' JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, June 1996 (1996-06), pages 2437-2448, XP002056313 ISSN: 0022-1007

D8: WO 97 41225 A (INCYTE PHARMA INC ;COLEMAN ROGER (US); WILDE CRAIG G (US); AU YOUN) 6 November 1997 (1997-11-06)

2) Novelty - Art.33(1) and (2) PCT:

Group 1: Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1-9.

Claims 1-9 appear to be new in light of the cited prior art, which nowhere discloses antisense oligonucleotides against the common sub-unit of the IL-3, IL-5 and GM-CSF receptors or their use in treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

Group 2: Combination of oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors and either against the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors: Claims 10-19 and 24-36.

Claims 10-19 and 24-36 appear to be new in light of the cited prior art, which nowhere discloses the combination of antisense oligonucleotides against the common sub-unit of the IL-3, IL-5 and GM-CSF receptors with antisense oligonucleotides directed at other chemokine receptors or their use in treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

Group 3: Combination of oligonucleotides directed against a nucleic acid encoding the CCR3 receptor and against the common subunit of the IL-4 and IL-13 receptors: Claims 20-23 and 37-40.

Claims 20-23 and 37-40 appear to be new in light of the cited prior art, which nowhere discloses the combination of antisense oligonucleotides against the common sub-unit of the IL-4 and IL-13 receptors with antisense oligonucleotides directed at the CCR3 receptor or their use in treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

3) **Inventive Step - Art.33(1) and (3) PCT**:

Group 1: Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1-9.

The closest prior art is document D4, which discloses an antagonist to the common subunit of the IL-3, IL-5 and GM-CSF receptors and its use in treating a number of medical conditions (page 7 lines 15-19; page 9 lines 20-23).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative method for inhibiting the activation of the IL-3, IL-5 and GM-CSF receptors.

The technical problem is solved by the subject matter of claims 1-9 which provide antisense oligonucleotides for the common subunit of these receptors and methods of treatment using these compositions.

Because antisense oligonucleotides directed against the common subunit of the IL-3, IL-5 and GM-CSF receptors are not taught in the prior art, the provision of such compounds and their employment must be regarded as demonstrating inventive step.

Group 2: Combination of oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors and either against the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors: Claims 10-19 and 24-36.

The closest prior art is document D4, which discloses an antagonist to the common subunit of the IL-3, IL-5 and GM-CSF receptors and its use in treating a number of medical conditions (page 7 lines 15-19; page 9 lines 20-23).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative method for inhibiting the allergic response.

The technical problem is solved by the subject matter of claims 10-19 and 24-36,

which provide the combination of antisense oligonucleotides for the common subunit of these receptors, of these antisense oligonucleotides with antisense oligonucleotides directed against either the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors and methods of treatment using these compositions.

Because antisense oligonucleotides directed against the common subunit of the IL-3, IL-5 and GM-CSF receptors are not taught in the prior art, the combination of these compounds with other antisense oligonucleotides and their employment is regarded as demonstrating inventive step.

Group 3: Combination of oligonucleotides directed against a nucleic acid encoding the CCR3 receptor and against the common subunit of the IL-4 and IL-13 receptors: Claims 20-23 and 37-40.

The closest prior art is document D1, which discloses antisense oligonucleotides to the CCR3 receptor and their use for therapeutic purposes (page 5 lines 14-18; page 57 lines 2-3 and 21-29).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative method for inhibiting the allergic response using antisense oligonucleotides.

The technical problem is solved by the subject matter of claims 10-19 and 24-36, which provide the combination of antisense oligonucleotides directed against the CCR3 receptor and the common subunit of the IL-4 and IL-13 receptors and methods of treatment using these compositions.

Because the cited prior art does not contain any motivation to combine antisense oligonucleotides against the CCR3 receptor and the common subunit of the IL-4 and IL-13 receptors, claims 10-19 and 24-36 are regarded as demonstrating inventive step.

4) **Industrial Applicability - Art.33(1) and (4) PCT**:

For the assessment of the present claims 5-7 and 24-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 13886	25.03.99	17.09.98	09.06.98

The above document discloses antisense oligonucleotides for, among other receptors, the IL-3 and IL-5 receptors (SEQ ID NOs. 1102-1115, 1159-1162, 1761-1763 and 1776-1779 and claim 10).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
13424-1pct		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00572	17/06/1999	17/06/1998
Applicant		
RECH. EXPERTISES ET DEV. MEDICAUX PARAENZ INC. et		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[X] None of the figures.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/CA 99/ 00572

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,5-9 (all partially) and claim 4

Antisense oligonucleotides directed against a nucleic acid encoding the CCR3 receptor, and defined by SEQ IDs 18, 20, 22 and 23. Their use in the preparation of pharmaceutical compositions for the treatment or the prevention of asthma, allergy, hypereosinophilia, inflammation or cancer.

2. Claims: 1,5-9 (all partially) and claim 2

Antisense oligonucleotides directed against a nucleic acid encoding the common sub-units of the IL-4 and IL-13 receptors, and defined by SEQ IDs 1 to 7. Their use in the preparation of pharmaceutical compositions for the treatment or the prevention of asthma, allergy, hypereosinophilia, inflammation or cancer.

3. Claims: 1,5-9 (all partially) and claim 3

Antisense oligonucleotides directed against a nucleic acid encoding the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors, and defined by SEQ IDs 9 to 16. Their use in the preparation of pharmaceutical compositions for the treatment or the prevention of asthma, allergy, hypereosinophilia, inflammation or cancer.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00572

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 A61K31/70 C07H21/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K C07H C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 22371 A (BRIGHAM & WOMENS HOSPITAL ;LEUKOSITE INC (US); PONATH PAUL D (US);) 25 July 1996 (1996-07-25) page 17, line 32 -page 18, line 19 page 23, line 10 -page 24, line 22 page 56, line 29 -page 64 claims 46-48 --- -/--	1,4,6-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2000	18. 02. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Andres, S

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	IKIZAWA K ET AL: "INHIBITION OF IL-4 RECEPTOR UP-REGULATION ON B CELLS ANTISENSE OLIGODEOXYNUCLEOTIDE SUPPRESSES IL-4-INDUCED HUMAN IGE PRODUCTION" CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 100, no. 3, 1995, pages 383-389, XP000561859 ISSN: 0009-9104 abstract page 384, left-hand column, line 9 - line 28 ---	1,2,5,7, 9
X	WO 97 20926 A (SANOFI SA ;CAPUT DANIEL (FR); FERRARA PASCUAL (FR); LAURENT PATRIC) 12 June 1997 (1997-06-12) page 3, line 7 -page 4, line 15 page 9, line 20 - line 29 examples 7-9 claims 24,25 ---	1,2,6-9
Y	WO 97 28190 A (MEDVET SCIENCE PTY LTD ;LOPEZ ANGEL (AU); BAGLEY CHRISTOPHER (AU);) 7 August 1997 (1997-08-07) page 7, line 15 -page 10, line 4 example 4 claims ---	1,3,6-9
Y	WO 97 23244 A (SMITHKLINE BEECHAM CORP ;WEN WU DING (US)) 3 July 1997 (1997-07-03) claims 5,6 page 4, line 29 -page 5, line 4 ---	1,3,6-9
X	WO 97 41154 A (DAUGHERTY BRUCE L ;DEMARTINO JULIE A (US); SICILIANO SALVATORE J () 6 November 1997 (1997-11-06) page 10, line 14 -page 13, line 13 ---	1,4,7,9
X	WO 97 22698 A (ICOS CORP) 26 June 1997 (1997-06-26) page 7, line 1 - line 11 page 11, line 24 -page 12, line 18 page 50, SEQ ID 4 ---	1,4,7,9
A	PONATH P D ET AL: "MOLECULAR CLONING AND CHARACTERIZATION OF A HUMAN EOTAXIN RECEPTOR EXPRESSED SELECTIVELY ON EOSINOPHILS" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, June 1996 (1996-06), pages 2437-2448, XP002056313 ISSN: 0022-1007 --- -/--	

4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 41225 A (INCYTE PHARMA INC ;COLEMAN ROGER (US); WILDE CRAIG G (US); AU YOUN) 6 November 1997 (1997-11-06) page 4, line 4 - line 25 page 22, line 7 -page 24, line 5 page 33, line 10 - line 18 claims 4,16,18,27 ---	1,4-9
A	DEVOS, R. ET AL.: "INTERLEUKIN-5 AND ITS RECEPTOR: A DRUG TARGET FOR EOSINOPHILIA ASSOCIATED WITH CHRONIC ALLERGIC DISEASE" JOURNAL OF LEUKOCYTE BIOLOGY, vol. 57, 1 June 1995 (1995-06-01), pages 813-819, XP002056891 ISSN: 0741-5400 the whole document ---	1,3,6-9
P,X	WO 99 13886 A (NYCE JONATHAN W ;UNIV EAST CAROLINA (US)) 25 March 1999 (1999-03-25) page 7, line 4 -page 9 page 19, line 4 -page 20, line 9 claims 1,2,10,29-42,52-58 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
/CA 99/00572

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9622371 A	25-07-1996	AU	688206 B	05-03-1998
		AU	5020296 A	07-08-1996
		AU	6994798 A	20-08-1998
		CA	2207086 A	25-07-1996
		EP	0828828 A	18-03-1998
		JP	10512753 T	08-12-1998
WO 9720926 A	12-06-1997	FR	2742156 A	13-06-1997
		AU	7576096 A	27-06-1997
		BR	9611697 A	17-02-1999
		CA	2238893 A	12-06-1997
		EP	0876482 A	11-11-1998
		JP	11511028 T	28-09-1999
		NO	982550 A	05-08-1998
WO 9728190 A	07-08-1997	AU	706462 B	17-06-1999
		AU	1536697 A	22-08-1997
		EP	0889905 A	13-01-1999
WO 9723244 A	03-07-1997	NONE		
WO 9741154 A	06-11-1997	NONE		
WO 9722698 A	26-06-1997	AU	1689297 A	14-07-1997
		BR	9607300 A	25-11-1997
		CA	2213331 A	26-06-1997
		CN	1183805 A	03-06-1998
		CZ	9702610 A	17-06-1998
		EP	0811063 A	10-12-1997
		HU	9801127 A	28-08-1998
		JP	11503028 T	23-03-1999
		NO	973800 A	20-10-1997
		PL	321937 A	05-01-1998
		SK	112897 A	08-07-1998
WO 9741225 A	06-11-1997	AU	2813297 A	19-11-1997
		CA	2252432 A	06-11-1997
		EP	0906424 A	07-04-1999
WO 9913886 A	25-03-1999	AU	9395198 A	05-04-1999
		WO	9963938 A	16-12-1999

studies of antisense oligonucleotides as therapeutic agents for cancer and viral diseases.

Few studies have been performed in order to assess whether antisense oligonucleotides could inhibit receptor expression on cell surfaces for inflammatory mediators.

Antisense oligonucleotides can be used to inhibit interleukin (IL)-6 receptor expression and thus the effects of the acute inflammatory mediator interleukin-6 on cells. No studies have been conducted to assess whether antisense oligonucleotides can be employed to inhibit receptors on cells that are involved in asthmatic inflammation or on cancerous cells.

Asthma is a disease that affects 5 to 10% of the population which has doubled in prevalence in the last 25 years. This increase has been noted especially in infants after a viral infection of the airways (bronchiolitis), in children and in occupational induced asthma. The exact cause of asthma is not yet known. However, it is believed that agents such as viruses are involved in the perpetuation of the abnormal inflammation that is found in the airways of patients with asthma and thus the persistence of the disease.

For this reason the current recommendations for first line therapy of asthma is a potent anti-inflammatory medication such as corticosteroids and antileukotrienes. Although this therapy is effective in many patients, some patients are resistant to corticosteroids. This medication is also a potent immunosuppressive with long term side effects and has not been shown to be effective in the prevention of allergy or asthma.

CCR3 receptor could inhibit the mRNA expression of this receptor on Ghost cells transfected with the CCR3 receptor. These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 21, gel on the right, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10μMol antisense. The gel on the left shows the results obtained for the housekeeping gene G3PDH.

Additional experiments were performed to assess whether antisense oligonucleotides directed against the CCR3 receptor could inhibit the function of this receptor. It is to be noted in Fig. 22 that the antisense oligonucleotide directed against the CCR3 receptor (RC269AS: 5'-CCCTGACATA GTGGATC-3' SEQ ID NO:20) and RC86A are effective at inhibiting calcium mobilization (a sign of chemotaxis) in eosinophils. Human eosinophils were purified from blood obtained from patients with asthma by Ficoll Hypaque centrifugation, red blood cell lysis, followed by negative selection with anti-CD16 coated magnetic beads on a MACS cell sorter (to eliminate neutrophils). The eosinophils were then washed and incubated with recombinant human IL-5 (1.6 ng/ml) in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, penicillin, streptomycin, and l-glutamine at 37°C in 5% CO_2 overnight. The cells were washed and then incubated in RPMI 1640 during 4 hours in the presence or absence of 10 μM RC269AS or 10μM RC269S 5'-GATCCACTAT GTCAGGG-3' (SEQ ID NO:21) washed and resuspended at 2.5x106 cells/ml in RPMI 1640 and incubated with Fura-2M at a concentration of 3μM for 45

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. An antisense oligonucleotide for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said oligonucleotide being directed against a nucleic acid sequence coding for a receptor selected from the group consisting of a CCR3 receptor, a common sub-unit of IL-4 and IL-13 receptors, and a common sub-unit of IL-3, IL-5 and GM-CSF receptors.

2. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common sub-unit of the IL-4 and IL-13 receptors.

3. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors.

4. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the sub-unit of the CCR3 receptor.

5. The oligonucleotide of claim 1, wherein said oligonucleotide has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, , SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ

ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:23.

6. A pharmaceutical composition for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said composition comprising at least one antisense oligonucleotide as defined in claim 1, 2, 3, 4 or 5, in association with a pharmaceutically acceptable carrier.

7. Use of an oligonucleotide as defined in claim 1, 2, 3, 4 or 5 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

8. Use of a pharmaceutical composition as defined in claim 6 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

9. A method for treating and/or preventing asthma, allergy, general inflammation or cancer, said method comprising the step of administering an effective amount of an oligonucleotide as defined in claim 1, 2, 3, 4 or 5, to a patient in need of such a treatment.

studies of antisense oligonucleotides as therapeutic agents for cancer and viral diseases.

Few studies have been performed in order to assess whether antisense oligonucleotides could inhibit receptor expression on cell surfaces for inflammatory mediators.

Antisense oligonucleotides can be used to inhibit interleukin (IL)-6 receptor expression and thus the effects of the acute inflammatory mediator interleukin-6 on cells. No studies have been conducted to assess whether antisense oligonucleotides can be employed to inhibit receptors on cells that are involved in asthmatic inflammation or on cancerous cells.

International Application published as WO9622371A (Ponath Paul D.) describes the C-C chemokine receptor CKR-3. It is the equivalent of the CCR3 receptor. In the application, there is no preliminary information on whether antisense constructs are effective at inhibiting the CCR-3 receptor. In addition there is no information on the fact that they are effective.

Ikizawa et al. "Inhibition of IL-4 receptor up-reulation on B cells antisense oligodeoxynucleotide suppresses IL-4-induced human IGE production" *Clinical and Experimental Immunology*, Vol. 100, No. 3, pp. 383-389, (1995)", describes antisense oligonucleotides against the IL-4 receptor. The re is no mention that this is against the common IL-4 IL-13 receptor. There is no discussion of the common effects with IL-13 or of synergy with IL-13. There is also no dicussion of the need to synergize by adding with other oligos.

International Application published as WO 97 20926, identified the IL-13 receptor alpha and beta sequences. They mention the term antisense oligonucleotides without providing any further information on any sequence or data.

International Application published as WO 9728190 describes the common Beta c receptor for IL-3, IL-5 and GM-CSF. There is nc description of the use of antisense oligos for the therapy of allergy, asthma or cancer in any part of the application.

International Application published as WO 97 23244 announces that ODNs are provided which are targeted to the nucleic acid encoding receptor negative regulatory domains. They are targeting genes that encode negative regulatory domains. They are looking at EPO.

International Application WO 97 41154 describes the eosinophil eotaxin receptor that has been designated "CC CKR3". Nowhere in the application is there any sequence or evidence of data for antisense oligonucleotides which can bind to eosinophil eotaxin receptor nucleotides and modulate receptor function or expression".

Ponath PD et al. "Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils" *Journal of Experimental Medicine*, Vol. 183, June 1996, pp. 2437-2448, (June 1996), only presents the eotaxin receptor CCR3 sequence.

International Application published as WO9741225A disclose polynucleotides against chemokine receptors for screening. Antisense ODNs are presented

against the MMLR-CCR or MPHG-CCR chemokine receptors and do not correspond to the receptors of the present invention.

Asthma is a disease that affects 5 to 10% of the population which has doubled in prevalence in the last 25 years. This increase has been noted especially in infants after a viral infection of the airways (bronchiolitis), in children and in occupational induced asthma. The exact cause of asthma is not yet known. However, it is believed that agents such as viruses are involved in the perpetuation of the abnormal inflammation that is found in the airways of patients with asthma and thus the persistence of the disease.

For this reason the current recommendations for first line therapy of asthma is a potent anti-inflammatory medication such as corticosteroids and antileukotrienes. Although this therapy is effective in many patients, some patients are resistant to corticosteroids. This medication is also a potent immunosuppressive with long term side effects and has not been shown to be effective in the prevention of allergy or asthma.

CCR3 receptor could inhibit the mRNA expression of this receptor on Ghost cells transfected with the CCR3 receptor. These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 21, gel on the right, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10μMol antisense. The gel on the left shows the results obtained for the housekeeping gene G3PDH.

Additional experiments were performed to assess whether antisense oligonucleotides directed against the CCR3 receptor could inhibit the function of this receptor. It is to be noted in Fig. 22 that the antisense oligonucleotide directed against the CCR3 receptor (RC269AS: 5'-CCCTGACATA GTGGATC-3' SEQ ID NO:20) and RC86A are effective at inhibiting calcium mobilization (a sign of chemotaxis) in eosinophils. Human eosinophils were purified from blood obtained from patients with asthma by Ficoll Hypaque centrifugation, red blood cell lysis, followed by negative selection with anti-CD16 coated magnetic beads on a MACS cell sorter (to eliminate neutrophils). The eosinophils were then washed and incubated with recombinant human IL-5 (1.6 ng/ml) in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, penicillin, streptomycin, and l-glutamine at 37°C in 5% CO_2 overnight. The cells were washed and then incubated in RPMI 1640 during 4 hours in the presence or absence of 10 μM RC269AS or 10μM RC269S 5'-GATCCACTAT GTCAGGG-3' (SEQ ID NO:21) washed and resuspended at $2.5x10^6$ cells/ml in RPMI 1640 and incubated with Fura-2M at a concentration of 3μM for 45

CLAIMS

1. An antisense oligonucleotide for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said oligonucleotide being directed against a nucleic acid sequence coding for a common subunit of the IL-3, IL-5 and GM-CSF receptors.

2. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors.

3 The oligonucleotide of claim 1, wherein said oligonucleotide has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, , SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:23.

4. A pharmaceutical composition for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said composition comprising at least one antisense oligonucleotide as defined in claim 1, 2 or 3, in association with a pharmaceutically acceptable carrier.

5. Use of an oligonucleotide as defined in claim 1, 2 or 3 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

6. Use of a pharmaceutical composition as defined in claim 4 for treating and/or preventing asthma,

allergy, hypereosinophilia, general inflammation or cancer.

7. A method for treating and/or preventing asthma, allergy, general inflammation or cancer, said method comprising the step of administering an effective amount of an oligonucleotide as defined in claim 1, 2 or 3, to a patient in need of such a treatment.

8. Use of an oligonucleotide as defined in claim 1, 2 or 3 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

9. Use of a pharmaceutical composition as defined in claim 4 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

10. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

11. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

12. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

13. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

14. The pharmaceutical composition according to claim 10, further comprising at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

15. The pharmaceutical composition according to claim 14, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

16. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

17. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

18. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

19. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

20. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

21. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

22. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

23. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

24. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

25. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

26. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

27. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed

against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

28. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors, at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

29. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

30. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

31. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

32. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO: 6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO: 20, SEQ ID NO:22, and SEQ ID NO:23.

33. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

34. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

35. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

36. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

37. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and

IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

38. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

39. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

40. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO;22, and SEQ ID NO:23.

ATENT COOPERATION TRE. Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
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in its capacity as elected Office

Date of mailing (day/month/year) 14 February 2000 (14.02.00)	
International application No. PCT/CA99/00572	**Applicant's or agent's file reference** 13424-1pct
International filing date (day/month/year) 17 June 1999 (17.06.99)	**Priority date** (day/month/year) 17 June 1998 (17.06.98)
Applicant RENZI, Paolo	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:
14 January 2000 (14.01.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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September 21, 2000

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European Patent Office
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Att.: M Page

International Patent Application
No. PCT/CA99/00572 – June 17, 1999
ANTISENSE OLIGONUCLEOTIDES FOR TREATING ATOPIC DISEASES AND NEOPLASTIC CELL PROLIFERATION"
Inventor: Paolo Renzi
Our ref.: 13424-1"PCT" CC/LM

Sir:

In response to the Written Opinion mailed June 21, 2000, in connection with the above-identified application, please consider the following amendments and remarks.

DISCLOSURE:

Please substitute pages 2 , 2a, 2b and 33 submitted herewith for pages 2 and 33 now on file.

CLAIMS:

Please substitute the pages containing claims 1 to 40 submitted herewith for the pages containing claims 1 to 9 now on file.

First of all, Applicant appreciates that the Examiner acknowledged the novelty of claims 3 and 5 and the inventive step of claim 3.

Novelty

In order to overcome the Examiner's rejection of claims 1, 4, and 6 to 9 with respect to the novelty of Group 1 of invention, the Examiner will note that

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International Preliminary Examination Authority

claim 1 has been amended to be restricted to the invention of Group 3. Moreover, former claim 4 has also been deleted and the dependency of former claims 6 to 9 has been amended accordingly.

In light of the above, it is respectfully submitted that the Examiner's rejection of claims 1, 4, and 6 to 9, with respect to Group 1 as not being novel in light of the prior art, is respectfully traversed.

Now turning to the Examiner's rejection of claims 1, 2, 6, and 7 to 9 with respect to Group 2 as not being novel in light of the prior art, Applicant wishes to point out that, as mentioned above, claim 1 has been amended to be restricted to Group 3 of invention. Moreover, former claim 2 has also been deleted. The dependency of former claims 6 and 7 to 9 has thus been amended accordingly.

From the above, the Examiner's rejection for lack of novelty of former claims 1, 6 and 7 to 9 with respect to Group 2 is respectfully traversed.

Now turning to Group 3, in the Written Opinion, the Examiner acknowledged that claims 1, 3, and 5 to 9 are novel with respect to invention of Group 3 in view of the prior art.

Inventive step

Claims 1, 5 to 9 and 4 have been rejected with respect to Group 1 as being rendered obvious over the prior art cited, and more particularly over document D1.

In this respect, Applicant wishes to point out that the prior claims on CCR3 receptor mentioned the term "antisense" but gave no experiments to back the claims. The Applicant has tried several antisense oligonucleotides directed against the CCR3 receptor that are not effective, such as SEQ ID NO:23 (CCR3A2) and two others directed against the human CCR3 receptor. Two effective antisense oligonucleotides are presented in the present application, i.e. RC86A (SEQ ID NO:18) and RC269AS (SEQ ID NO:20). Although both were effective at inhibiting calcium mobilization in eosinophils, RC269AS was much less effective at inhibiting the CCR3 receptor on GHOST cells transfected with the CCR3 receptor (see Fig. 1). These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 1, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10µMol of antisense. However, the antisense

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oligonucleotide RC269AS at a concentration of 10µMol was not effective (on the right). The methods for these experiments are described in the patent application. From the above, it can be seen that not all antisense oligonucleotides are effective for treating and/or preventing asthma, allergies, hypereosinophilia, general inflammation or cancer. Only some of them are effective. Therefore, despite SEQ ID NO:3 disclosed in document D1, one skilled in the art could not have arrived at the antisense oligonucleotides as now claim in the present application without involving inventive skills. Accordingly, it is respectfully submitted that former claims 1, 5 to 9 and 4 are inventive over document D1.

With respect to the inventive activity of claims 1, 5 to 9 and claim 2 with respect to Group 2, Applicant notes that all these sequences (SEQ ID NOS:1 to 7 as disclosed in the present application) have the advantage of inhibiting expression of both IL-4 and IL-13. In rejecting the claims for obviousness, the Examiner has cited document D2. However, document D2 did not look at inhibiting both IL-4 and IL-13, but only wanted to inhibit IL-4 alone. Nowhere in his document D1 is there a suggestion or teaching that an attempt was made to inhibit the effects of both mediators. Throughout document D1, the inventor had mentioned only the IL-4 receptor. It is thus the belief of authors of document D2 and within the prior art that inhibition of the IL-4 receptor was sufficient to prevent the production of IgE. Accordingly, Applicant does not believe that document D2 is relevant to the present application as it does not address the inhibition of IL13 mediator. Moreover, the sequences of the antisense oligonucleotides of the present invention, directed towards human common IL-4R and IL-13R receptors chain are different from the antisense disclosed in document D2. Three antisense phosphorothioate oligonucleotides were designed by the authors of document D2 against nucleotides 174-190 (S-oligo 1 : GAG CCC AGA GCA AAG CCA CCC CAT), 199-220 (S-oligo 2 : AGG CAG CTC ACA GGG AAC AG) and 238-258 (S-oligo 3 : ACC TTC ATG TTC CCA GAG CT). S-oligo 1 and S-oligo 2 inhibited the constitutive expression of IL-4 receptor on Daudi cells, while the S-oligo 3 was not effective. Furthermore, only S-oligo 1 was used in all experiments since it displayed the strongest inhibition of the IL-4R expression.

In clear contrast, in the present application, 7 oligonucleotides have been designed against the common receptors for IL-4 and IL-13. Three of these oligonucleotides were on the sub-unit studied by the authors of document D2. Our 3 effective antisense oligonucleotides are directed against nucleotides 241-260 (OD1: 5'AGA CCT TCA TGT TCC CAG AG 3'), 231-250 (OD2: 5' AGG TGG CAA GCT CTG GGA AC 3') and 248-266 (OD3: 5' CCT GCA AGA CCT TCA TGT T 3'). Although OD1, OD2, OD3 and S-oligo 3 are

overlapping, the authors of document D2 said that S-oligo 3 was not effective (in the same region where the present inventor has designed his effective oligonucleotides). Since the prior art states that the region where the inventor of the present application has designed the antisense is ineffective and since all the antisense oligonucleotides of the present application are in clear contradiction effective, it is respectfully submitted that results presented in the present application are surprising and inventive over document D2. In any event, the Examiner has rejected as mentioned previously, claims 1, 5 to 9 and 4 for lack of inventive activity. However, claim 1 has been restricted to Group 3 of invention, and claim 4 has been deleted. Accordingly, the above argumentation does therefore apply to former claims 5 to 9 now corresponding to new claims 3 to 7.

In view of the above and foregoing, it is respectfully submitted that the claims now on file are clearly inventive over document D2 with respect to Group 2 of invention.

Now turning to Group 3 of invention with respect to inventive activity, the Examiner has acknowledged in the Written Opinion on sheet 5, that claims 1, 3 and 5 to 9 were inventive with respect to Group 3 of invention over the prior art cited.

Industrial applicability

Despite the fact that the Examiner has mentioned that there is no unified criteria existing in the PCT contracting states for assessing the industrial applicability of former claims 7 to 9, now corresponding to claims 5 to 7, Applicant preferred nevertheless to maintain these claims in the application as these might be found allowable in some PCT contracting states.

Re Item VII

In order to comply with Rule 5.1(a)(II) PCT, page 2 of the disclosure has been amended in order to incorporate a brief discussion of documents D1 to D8 as required by the Examiner.

Furthermore, page 33 of the description has been corrected with respect to the mis-printed cell amounts.

As the Examiner will note, after overcoming all of the Examiner's rejections, new claims have been introduced that also are believed to be novel and inventive over the prior art cited, which relates to synergy between two different antisense targeting two different receptors. These claims are clearly

supported by the application as originally filed. More particularly, the application as originally filed has already shown that synergy exist between mediators; see Fig. 24 from the patent which shows that priming with IL-5 increases the chemotactic response of eosinophils to eotaxin. It is also reported that the CCR3 receptor is present on eosinophil progenitors (CD34 positive cells) and is involved in eosinophil differentiation. All the ligands that act through the CCR3 receptor synergize with IL-5 to increase eosinophil differentiation.

In the present application, it was also shown that synergy can occur between the antisense oligonucleotides directed against CCR3 and the common Beta-receptor for IL-3, IL-5 and GM-CSF *in vivo* in rats (see Fig. 18B). The dose employed was pre-treatment with 500 µg of ODN intra-peritoneally followed by 200µg of ODN intra-tracheally at the time of antigen challenge. From the above, and more specifically from the results provided in the application as originally filed, there is clear evidence of synergistic effects of a combination of the antisense of the present invention *in vitro* on human cells and *in vivo* in rats (the eosinophilic response after antigen challenge and airway responsiveness to leukotriene D4). There is also evidence in the application that with the antisense of the present invention, it is now possible to convert a non-responder rat into a responder rat. The synergistic effect of combination antisense therapy is not taught or even remotely suggested in the prior art. For example, there is no published information showing the CCR3 receptor, the common Bc receptor or their ligands are involved in TH2 cell differentiation . The simultaneous blockage of genes is contrary to industry practice. Indeed, a non-exhaustive list of programs directed against mediators for the therapy of asthma includes: therapies against one mediator or the use of only one mediator. The combination antisense therapy as suggested in the present application has many advantages that are not even suspected in the prior art, such that it can inhibit the effect of up to 8 mediators.

Therefore, in order to protect these various possible combinations that would allow for synergy of the antisense oligonucleotide of the present invention, new claims 10 to 40 have been added. These claims are originally supported by the description and therefore, no new matter is being hereby introduced. Furthermore, claims 8 and 9 have been introduced. These claims are in the format of Swiss-type use claims which correspond in scope to former claims 7 and 8, now corresponding to claims 5 and 6.

The Examiner will find the specific portion of the application that supports these claims in the Index.

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In view of the above, it is respectfully submitted that all the claims now on file have novelty, inventive step and industrial applicability over the D1 and D8 references identified in the Written Opinion.

It is believed that the Office is now in a position to provide a positive opinion with respect to the claims.

Favourable consideration and a positive International Preliminary Examination Report are requested.

Respectfully submitted,

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Enc. Pages 2, 2a, 2b and 33 of the disclosure
Claims 1 to 40;
Figure 1 of the drawings;
Index; and
EPO 1037.

studies of antisense oligonucleotides as therapeutic agents for cancer and viral diseases.

Few studies have been performed in order to assess whether antisense oligonucleotides could inhibit receptor expression on cell surfaces for inflammatory mediators.

Antisense oligonucleotides can be used to inhibit interleukin (IL)-6 receptor expression and thus the effects of the acute inflammatory mediator interleukin-6 on cells. No studies have been conducted to assess whether antisense oligonucleotides can be employed to inhibit receptors on cells that are involved in asthmatic inflammation or on cancerous cells.

International Application published as WO9622371A (Ponath Paul D.) describes the C-C chemokine receptor CKR-3. It is the equivalent of the CCR3 receptor. In the application, there is no preliminary information on whether antisense constructs are effective at inhibiting the CCR-3 receptor. In addition there is no information on the fact that they are effective.

Ikizawa et al. "Inhibition of IL-4 receptor up-reulation on B cells antisense oligodeoxynucleotide suppresses IL-4-induced human IGE production" *Clinical and Experimental Immunology*, Vol. 100, No. 3, pp. 383-389, (1995)", describes antisense oligonucleotides against the IL-4 receptor. The re is no mention that this is against the common IL-4 IL-13 receptor. There is no discussion of the common effects with IL-13 or of synergy with IL-13. There is also no dicussion of the need to synergize by adding with other oligos.

International Application published as WO 97 20926, identified the IL-13 receptor alpha and beta sequences. They mention the term antisense oligonucleotides without providing any further information on any sequence or data.

International Application published as WO 9728190 describes the common Beta c receptor for IL-3, IL-5 and GM-CSF. There is no description of the use of antisense oligos for the therapy of allergy, asthma or cancer in any part of the application.

International Application published as WO 97 23244 announces that ODNs are provided which are targeted to the nucleic acid encoding receptor negative regulatory domains. They are targeting genes that encode negative regulatory domains. They are looking at EPO.

International Application WO 97 41154 describes the eosinophil eotaxin receptor that has been designated "CC CKR3". Nowhere in the application is there any sequence or evidence of data for antisense oligonucleotides which can bind to eosinophil eotaxin receptor nucleotides and modulate receptor function or expression".

Ponath PD et al. "Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils" *Journal of Experimental Medicine*, Vol. 183, June 1996, pp. 2437-2448, (June 1996), only presents the eotaxin receptor CCR3 sequence.

International Application published as WO9741225A disclose polynucleotides against chemokine receptors for screening. Antisense ODNs are presented

against the MMLR-CCR or MPHG-CCR chemokine receptors and do not correspond to the receptors of the present invention.

Asthma is a disease that affects 5 to 10% of the population which has doubled in prevalence in the last 25 years. This increase has been noted especially in infants after a viral infection of the airways (bronchiolitis), in children and in occupational induced asthma. The exact cause of asthma is not yet known. However, it is believed that agents such as viruses are involved in the perpetuation of the abnormal inflammation that is found in the airways of patients with asthma and thus the persistence of the disease.

For this reason the current recommendations for first line therapy of asthma is a potent anti-inflammatory medication such as corticosteroids and antileukotrienes. Although this therapy is effective in many patients, some patients are resistant to corticosteroids. This medication is also a potent immunosuppressive with long term side effects and has not been shown to be effective in the prevention of allergy or asthma.

CCR3 receptor could inhibit the mRNA expression of this receptor on Ghost cells transfected with the CCR3 receptor. These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 21, gel on the right, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10μMol antisense. The gel on the left shows the results obtained for the housekeeping gene G3PDH.

Additional experiments were performed to assess whether antisense oligonucleotides directed against the CCR3 receptor could inhibit the function of this receptor. It is to be noted in Fig. 22 that the antisense oligonucleotide directed against the CCR3 receptor (RC269AS: 5'-CCCTGACATA GTGGATC-3' SEQ ID NO:20) and RC86A are effective at inhibiting calcium mobilization (a sign of chemotaxis) in eosinophils. Human eosinophils were purified from blood obtained from patients with asthma by Ficoll Hypaque centrifugation, red blood cell lysis, followed by negative selection with anti-CD16 coated magnetic beads on a MACS cell sorter (to eliminate neutrophils). The eosinophils were then washed and incubated with recombinant human IL-5 (1.6 ng/ml) in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, penicillin, streptomycin, and l-glutamine at 37°C in 5% CO_2 overnight. The cells were washed and then incubated in RPMI 1640 during 4 hours in the presence or absence of 10 μM RC269AS or 10μM RC269S 5'-GATCCACTAT GTCAGGG-3' (SEQ ID NO:21) washed and resuspended at $2.5x10^6$ cells/ml in RPMI 1640 and incubated with Fura-2M at a concentration of 3μM for 45

CLAIMS

1. An antisense oligonucleotide for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said oligonucleotide being directed against a nucleic acid sequence coding for a common subunit of the IL-3, IL-5 and GM-CSF receptors.

2. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors.

3 The oligonucleotide of claim 1, wherein said oligonucleotide has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, , SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:23.

4. A pharmaceutical composition for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said composition comprising at least one antisense oligonucleotide as defined in claim 1, 2 or 3, in association with a pharmaceutically acceptable carrier.

5. Use of an oligonucleotide as defined in claim 1, 2 or 3 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

6. Use of a pharmaceutical composition as defined in claim 4 for treating and/or preventing asthma,

allergy, hypereosinophilia, general inflammation or cancer.

7. A method for treating and/or preventing asthma, allergy, general inflammation or cancer, said method comprising the step of administering an effective amount of an oligonucleotide as defined in claim 1, 2 or 3, to a patient in need of such a treatment.

8. Use of an oligonucleotide as defined in claim 1, 2 or 3 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

9. Use of a pharmaceutical composition as defined in claim 4 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

10. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

11. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

12. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

13. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

14. The pharmaceutical composition according to claim 10, further comprising at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

15. The pharmaceutical composition according to claim 14, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

16. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

17. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

18. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

19. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

20. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

21. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

22. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

23. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

24. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

25. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

26. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

27. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed

against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

28. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors, at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

29. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

30. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

31. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

32. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO: 6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO: 20, SEQ ID NO:22, and SEQ ID NO:23.

33. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

34. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

35. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

36. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

37. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and

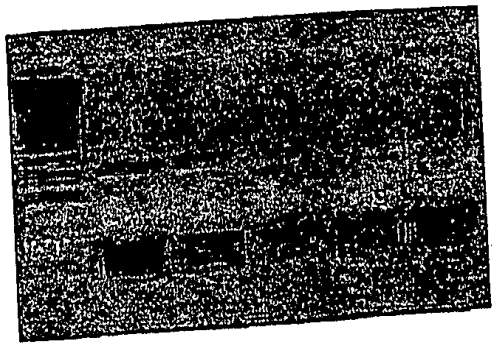
IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

38. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

39. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

40. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO;22, and SEQ ID NO:23.

Figure 1: PCR Test of 2 different CCR3 Antisense ODN 's on U937 cells



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INDEX

Original Claim No.	Action	New Claim No.	Supported
1	amended	1	Original claim 1
2	deleted		
3	amended	2	Original claim 3
4	deleted		
5	amended	3	Original claim 5
6	amended	4	Original claim 6
7	amended	5	Original claim 7
8	amended	6	Original claim 8
9	amended	7	Original claim 9
10	New	10	Original claims 7 and 8
11	New	11	Original claims 7 and 8
12	New	12	Original claims 1 and 5
13	New	13	Original claims 1 and 5
14	New	14	Original claim 4
15	New	15	Original claim 5
16	New	16	Original claims 3 and 4
17	New	17	Original claims 3, 4, and 5
18	New	18	Original claims 3, 4 and 5
19	New	19	Original claims 3, 4 and 5
20	New	20	Original claims 2 and 4

21	New	21	Original claims 2, 4 and 5
22	New	22	Original claims 2, 4 and 5
23	New	23	Original claims 2, 4 and 5
24	New	24	Original claims 2, 3 and 9
25	New	25	Original claims 2, 3, 5 and 9
26	New	26	Original claims 2, 3, 5 and 9
27	New	27	Original claims 2, 3, 5 and 9
28	New	28	Original claims 2, 3, and 9
29	New	29	Original claims 2, 3, 5 and 9
30	New	30	Original claims 2, 3, 5 and 9
31	New	31	Original claims 2, 3, 5 and 9
32	New	32	Original claims 5 and 9
33	New	33	Original claims 3 and 4
34	New	34	Original claims 3, 4, 5 and 9
35	New	35	Original claims 3, 4, 5 and 9
36	New	36	Original claims 3, 4, 5 and 9
37	New	37	Original claims 2, 4 and 9

38	New	38	Original claims 2, 4 and 9
39	New	39	Original claims 2, 4 and 9
40	New	40	Original claims 2, 4 and 9

PCT REQUEST

Original (for **SUBMISSION**) - printed on 16.06.1999 05:32:35 PM

0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.84 (updated 01.06.1999)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Canadian Patent Office (RO/CA)
0-7	**Applicant's or agent's file reference**	13424-1pct
I	**Title of invention**	ANTISENSE OLIGONUCLEOTIDES FOR TREATING OR PREVENTING ATOPIC DISEASES AND NEOPLASTIC CELL PROLIFERATION
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	**Applicant** This person is: Applicant for Name Address: State of nationality State of residence Telephone No. Facsimile No.	applicant only all designated States except US RECHERCHES EXPERTISES ET DÉVELOPPEMENT MÉDICAUX PARENZ INC. 38 Edgehill Road Westmount, Québec H3Y 1E9 Canada CA CA 514-281-6000 514-896-4677
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	applicant and inventor US only RENZI, Paolo 38 Edgehill Road Westmount, Québec H3Y 1E9 Canada CA CA

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	SWABEY OGILVY RENAULT
IV-1-2	Address:	Suite 1600 1981 McGill College Avenue Montreal, Québec H3A 2Y3 Canada
IV-1-3	Telephone No.	514-845-7126
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IV-1-5	e-mail	fcote@mtl.swabey.com
IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	CÔTÉ, France; MITCHELL, Robert; HOULE, Guy, J.; MARCOUX, Paul; MURPHY, Kevin, P.; CARRIER, Robert; SOFIA, Michel; ANGLEHART, James; NADEAU, François
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

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V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	17 June 1998 (17.06.1998)	
VI-1-2	Number	2,235,420	
VI-1-3	Country	CA	
VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description (excluding sequence listing part)	39	-
VIII-3	Claims	2	-
VIII-4	Abstract	1	abstract.txt
VIII-5	Drawings	31	-
VIII-6	Sequence listing part of description	6	-
VIII-7	TOTAL	83	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-15	Nucleotide and/or amino acid sequence listing in computer readable form		separate diskette
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**	1	
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	CÔTÉ, France	
IX-2	**Signature of applicant or agent**		
IX-2-1	Name	SWABEY OGILVY RENAULT	

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	